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Copper-catalyzed domino reaction between terminal alkynes, isocyanates, and oxiranes: An atom-economic route to morpholine derivatives

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Abstract

In situ generated copper acetylides react with isocyanates and oxiranes to form a decent range of morpholine derivatives. The reactions proceeded with acceptable yields and excellent regioselectivity. The presence of oxygen and moisture completely inhibited the reaction. The scope of the reaction is wide and the reactions involve consecutive C–C, C–N, and C–O bond formations.

1 | INTRODUCTION

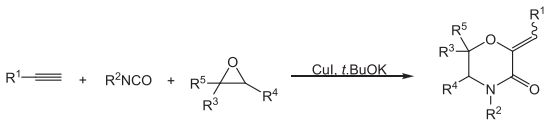
Reactions involving electrophilic cyclization across C–C triple bonds are known as reliable and valuable strategy for synthesis of a diverse range of heterocyclic compounds.[1,2] Along this line, those reactions involving domino nucleophilic addition–electrophilic cyclization catalysis in copper have preeminence.[3–6] The use of copper salts presents the advantages of being inexpensive, easy to handle, and insensitive, suitable for performing even in aqueous conditions. The role of copper is multifaceted in these reactions. Initially π–electrons of triple bond coordinated to copper salt, lowering the pK_a of alkyne proton to some extent in which easily removed by common bases.[7,8] In electrophilic cyclization, coordination of copper salts with the triple bond electrons led to develop a large partial positive charge ready for the *6-endo*, *6-exo*, and kinetically favored *5-exo* cyclizations.[9,10]Pioneered by Carreira in the 2000s, *in situ* metalation of terminal acetylenes and their reactions with various electrophiles attracted considerable attentions.[11–14] These reports revealed that copper acetylides could easily attack on carbonyls, imines, and even unsaturated carbonyl acceptors in mild reaction conditions and a benign solvent. Commencing from these reports, a number of reports involving nucleophilic additions of copper acetylides on C=N and C=O in the presence of an appropriate third partner electrophile have been appeared.[15–18] Particularly in this regard is the use of heterocumulenes and three-membered heterocycles in reaction with metal acetylides which opened up a possibility for expedient synthesis of a wide range of heterocyclic compounds from the readily available starting materials.[19–24] The reactions represent a meaningful step forward in leveraging the less-explored copper acetylide–heterocumulene coupling, both in terms of employing more practical catalysts and in incorporating an appropriate partner to access synthetically important

targets. On the other hand, Patel and coworkers have reported regioselective ring opening of three-membered heterocycles with aroyl isothiocyanates.[25,26]

Morpholine skeletons are common in pharmaceuticals and natural products and numerous synthetic approaches to access morpholine derivatives have been reported in literature.[27–29] To our knowledge no report on nucleophilic additions of copper acetylides on isocyanate has been reported in literature. Accordingly, we became encouraged to examine if isocyanate underwent nucleophilic additions with copper acetylides. Along this line, we report herein, regioselective ring opening of oxiranes with propargylic amide adduct derived from copper acetylides and isocyanates, leading to the formations of morpholine skeletons through a *6-exo* cyclization mode (Scheme 1).

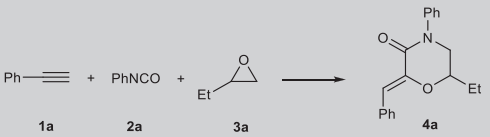
2 | PLACEHOLDER TEXTRESULTS AND DISCUSSION

An initial study on feasibility of the proposed reaction has been performed using phenyl acetylene (**1a**), phenyl isocyanate (**2a**), and 2-ethyloxirane (**3a**) in the presence of CuI as the catalyst and $(i\text{-Pr})_2$EtN as the base in MeCN. After the mixture being stirred at 105°C for 18 h, the desired compound **4a** was obtained only in traces amounts together with phenylcarbamic acid (derived from the hydrolysis of isocyanate) in 63% yield. Gratefully, performing the reaction with 3 Å molecular sieves not only completely suppress the formation of phenylcarbamic acid but also increased the yield of **4a** to 23%. To further develop the reaction parameters, we examined the reaction with various bases, solvents, and catalyst and the results are shown in Table 1. In initial effort, the reaction was performed with various organic and inorganic bases and *t*.BuOK gave superior result (entries 1–7). Of the solvents, dioxane has been found to be the most effective choice for the reaction (entries 8–12). It is worth mentioning that, PEG-400 (a known solvent in activation of oxiranes[30]) was not suitable here (entry 9). A catalyst survey indicated that the outcome of the reaction had great dependence to catalyst of choice (entries 13–20). However, the oxidation state of copper did not have appreciable effect on reaction yield (entry 17 *vs*. 18). The desired compound **4a** was formed only in low yield with AgOAc, suggesting the proposed reaction



SCHEME 1 Catalytic synthesis of morpholine derivatives.

TABLE 1 Optimization of reaction conditions[a]



Entry	Catalyst	Base	Solvent	Yield of 4 (%)
1	CuI	DIPEA	Dioxane	37
2	CuI	DBU	Dioxane	69
3	CuI	DABCO	Dioxane	31
4	CuI	Et_3N	Dioxane	21
5	CuI	Cs_2CO_3	Dioxane	47
6	CuI	*t*.BuOLi	Dioxane	25
7	CuI	*t*.BuOK	Dioxane	79
8	CuI	*t*.BuOK	DMF	38
9	CuI	*t*.BuOK	PEG-400	NR[b]
10	CuI	*t*.BuOK	MeCN	62
11	CuI	*t*.BuOK	Toluene	72
12	CuI	*t*.BuOK	THF	55
13	CuCl	*t*.BuOK	Dioxane	41
14	$CuBr.SMe_2$	*t*.BuOK	Dioxane	68
15	Cu_2O	*t*.BuOK	Dioxane	24
16	Cu $(CH_3CN)_4PF_6$	*t*.BuOK	Dioxane	80
17	CuOTf	*t*.BuOK	Dioxane	37
18	Cu $(OTf)_2$	*t*.BuOK	Dioxane	40
19	Cu $(OAc)_2$	*t*.BuOK	Dioxane	53
20	Cu $(BF_4)_2$	*t*.BuOK	Dioxane	62
21	AgOAc	*t*.BuOK	Dioxane	19
22	-	*t*.BuOK	Dioxane	Traces
23	CuI	-	Dioxane	-
24	CuI	*t*.BuOK	-	Traces

[a]Reaction conditions: **1a** (1.2 mmol), **2a** (1.0 mmol), **3a** (1.5 mmol), catalyst (0.1 mmol), 250 mg of ground 3 Å molecular sieves, base (1.5 mmol), and solvent (4.0 mL) at 105°C for 18 h.

[b]No reaction.

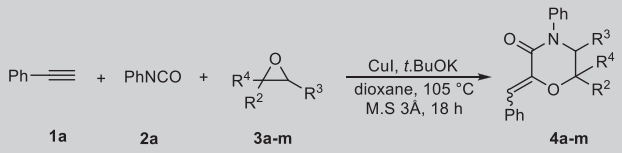
is not catalyzed by silver salts (entry 21). The reaction did not afford the targeted product **4a** in the absence of catalyst (entry 22). The reaction did not proceed at all without *t*.BuOK, indicating the vital role of base in this transformation (entry 23). Only a trace amount of the product **4a** was obtained under the neat condition (entry 24). Interestingly and in contrast of the previous reports, the reaction exhibited excellent chemoselectivity and no products arising from the direct attack of copper acetylide on **3a** are detected in crude reaction mixture analysis.[21,31] Based on the spectroscopic analyses, all of the reactions proceeded through a *6-exo* cyclization path.

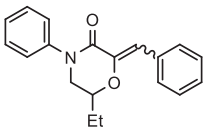
When the temperature was decreased to 80°C, the yield of **4a** dropped to 51% (not shown in Table 1). Additionally, decreasing the loading of the catalyst and base resulted in diminished yields (not shown in Table 1).

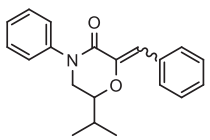
We next investigated the behavior of various oxiranes under the optimized reaction conditions (Table 2). Simple ethyl-linked oxirane **3a** afforded expected product **4a** in acceptable yield. It is worth mentioning that sterically encumbered oxiranes likes **3b** and **3c** reacted with only marginally decreased reaction yields. The proposed reaction is consistent with the presence of an ester as motif on oxirane, giving the desired products **4d** and **4e** with moderate yields. Oxiranes bearing an additional oxygen atom (an etheric group) likes **3f** and **3 g** afforded excellent yields of products **4f** and **4 g**, most likely due to a better coordination ability compared to that of other oxiranes. The reaction was found to tolerate cyclic oxirane **3 h**. Benzyl-linked oxirane **3i** was also effective in this transformation and gave the desired product **4i** in 79% yield. The regioselectivity in ring opening of oxirane completely switched upon using aromatic oxiranes under an otherwise identical reaction conditions, as aryl-substituted oxiranes **3j**–**3 m** afforded the benzylic-attacked products **4j**–**4 m**, exclusively. Importantly, the reactions with aromatic oxiranes also afforded comparatively higher yields than those of alkyl oxiranes. Interestingly, the tolerance for bromide moiety on the aromatic oxirane **3 m** offers an opportunity for subsequent cross-coupling reactions, giving further advantage to the present protocol from a synthetic point of view. This result indicated that π–electrons of the phenyl group of the oxirane might involve in reaction progress through coordination to the copper catalyst.

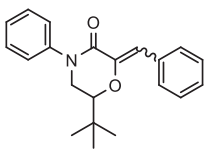
The reaction generality was also examined with various alkynes and isocyanates (Table 3). A modest increase in the yields of the products **4n** and **4o** occurred upon using alkyl-substituted isocyanates **2b** and **2c**. The presence of electron-realizing groups such as *p*-Me and *p*-methoxy on the phenyl ring of isocyanate afforded the targeted products **4q** and **4r** in 87 and 92% yields, compared to phenyl isocyanate **4p**, 80%. The reactivity of electron-rich alkyne **1c** was also tested with electron-neutral and electron-deficient aryl isocyanates **2a** and **2f**, providing the corresponding products **4 s** and **4 t** in

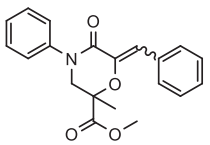
TABLE 2 Scope of oxirane[a]

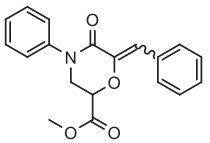


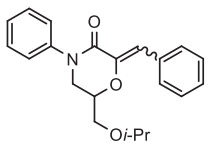

4a, 79%

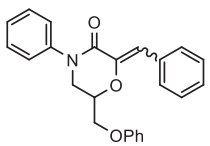

4b, 75%

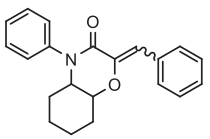

4c, 74%

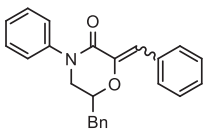

4d, 58%

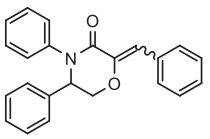

4e, 64%

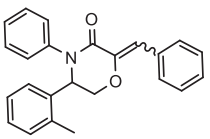

4f, 93%

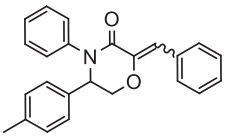

4g, 95%

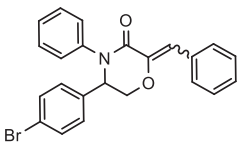

4h, 84%


4i, 79%


4j, 93%

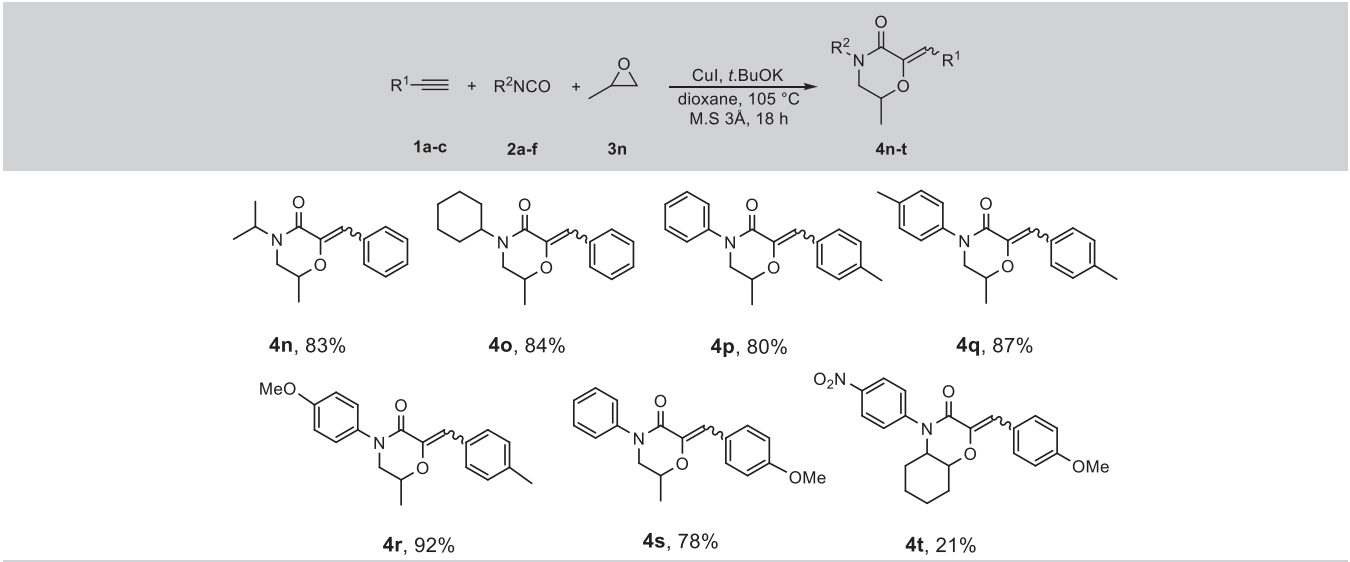

4k, 52%


4l, 93%


4m, 94%

[a]For all entries: **1a** (1.2 mmol), **2a** (1.0 mmol), **3** (1.5 mmol), CuI (0.1 mmol), *t*.BuOK (1.5 mmol), and 250 mg of ground 3 Å molecular sieves, in dry dioxane (4.0 mL) at 105°C for 18 h.

TABLE 3 Scope of alkyne and isocyanate[a]



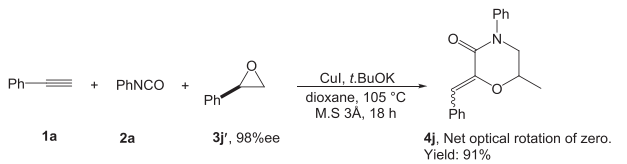
[a]For all entries except stated otherwise: **1** (1.2 mmol), **2** (1.0 mmol), **3n** (1.5 mmol), CuI (0.1 mmol), *t*.BuOK (1.5 mmol), and 250 mg of ground 3 Å molecular sieves, in dry dioxane (4.0 mL) at 105°C for 18 h.

[b]At 120°C for 22 h.

78% and 21% yields, respectively. These results demonstrated that the reaction outcome depends highly on electronic properties of phenyl isocyanates.

To further explore the reaction pathway chiral oxirane **3f'** was treated with phenyl isocyanate (**2a**) and ethyl oxirane (**3a**). This result indicated that the domino ring opening/cyclization reaction proceeded with racemization at the chiral carbon in the presence of phenyl oxirane (Scheme 2).

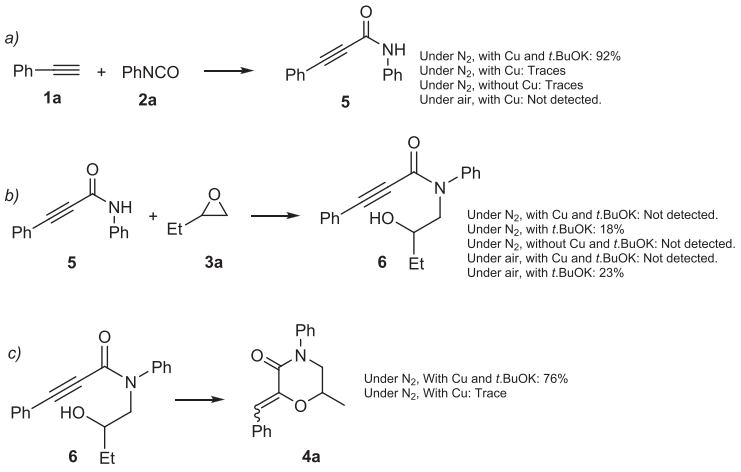
To get insight on the detail of the reaction pathway, the reaction was conducted in stepwise manner and the results are shown in Scheme 1. Initially, phenyl acetylene was reacted with phenyl isocyanate to form the expected propargylic amide **5**. The study indicated that the presence of copper salt and an inert atmosphere are necessary to furnish the transformation in acceptable yield (Scheme 3, *a*). For ring opening of oxirane with propargylic amide **5**, it would be interesting to see if copper salt is involved in reaction progress. To check this, the reaction was conducted with and without copper catalyst under an inert atmosphere and air (Scheme 3, *b*). Compound **6** could be isolated only in 18% yield without of catalyst while, no formation of the ring-opened intermediate **6** take place with copper salt and *t*.BuOK and instead the desired product **4a** was obtained in 78% yield. This data demonstrated that copper catalyst is involved in formation of compound **6**, presumably through electrophilic activation of oxirane. This proposal is supported by the fact that oxiranes bearing an etheric group, which could be act as an additional coordination site, reacted with higher yields (see Table 2, entries 6 and 7). Finally, the successes of electrophilic cyclization of alkynol **6** to morpholine skeleton **4a** had great dependence on the presence of copper catalyst as only a traces amount of **4a** was achieved in the absence of copper (Scheme 3, *c*).



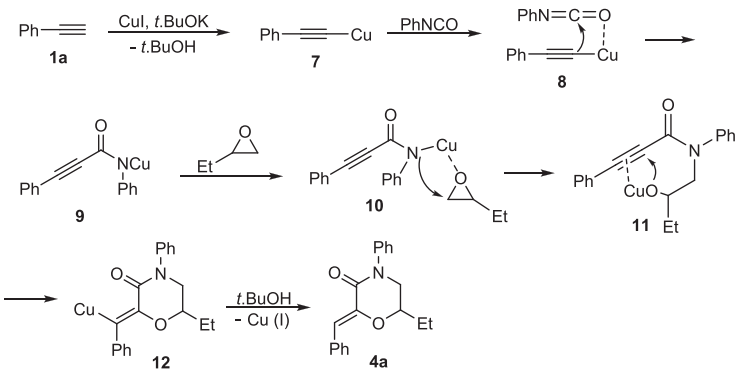
SCHEME 2 Enantiopure 2-phenyloxirane reaction.

Based on the above finding and commencing from previous reports, the following reaction pathway is proposed (Scheme 4). Coordination of copper catalyst with phenyl acetylene in the presence of *t*.BuOK gave copper acetylide **7**. The nucleophilic attack of *in situ* generated copper acetylide to the sp-carbon of isocyanate yielded the propargylic adduct **9** which further reacted with activated oxirane (species 10) to form the ring opened-intermediate **11**. The electrophilic cyclization of **11** by the action of copper salt afforded the expected *6-exo* intermediate **12** which further transferred to the compound **4a** by protonolysis with *t*.BuOH.

In this report, we have developed a novel catalytic reaction to form a range of morpholine derivatives from the commercially available substrates. Control experiments were performed to propose a more sophisticated reaction pathway. To furnish the transformation with good success, it is necessary to work under the conditions where oxygen and moisture are rigorously excluded. The



SCHEME 3 Control experiments.



SCHEME 4 Proposed mechanism.

effects of electronic and steric variations of substrates on reaction outcome have been examined. The regioselectivity in ring opening of oxiranes is switched upon using aryl-oxiranes however, in all cases the reactions proceeded in regioselective manner and only one regioisomer is detected in crude reaction mixture analysis.

3 | PLACEHOLDER TEXTEXPERIMENTAL

All reactions were carried out in Schlenk tube (25 mL) under an Ar atmosphere. All the reagents, catalysts, and additives were obtained from commercial sources. All the solvents were purchased from PALAENERGY Pure Chemical Industries, and were dried and degassed before use. Melting points were measured with Electrothermal-9100 apparatus. IR spectra were determined on a Nicolet 6700 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded with Bruker DRX-500 AVANCE instrument; in $CDCl_3$ at 500 and 125 MHz, resp; δ in ppm, J in Hz. Mass spectra were determined on a EIMS (70 eV): Finnigan-MAT-8430 mass spectrometer, in m/z. Elemental analyses were performed with a Heraeus Rapid analyzer. The results agreed favorably with the calculated values. Silica gel 60 (particle size 63–200 μm or 40–100 mesh) was used for column chromatography (Merck, item number 7734–3). TLC analyses were performed on commercial glass plates bearing a 0.25-mm layer of Merck Silica gel 60 (Merck, item number 116835).

3.1 | General procedure for the preparation of compounds 4

A Schlenk tube (25 mL) equipped with a magnetic stir bar was charged with terminal alkyne (1.2 mmol), isocyanate (1.0 mmol), CuI (0.1 mmol), *t*.BuOK (1.5 mmol), 250 mg of ground 3 Å molecular sieves, and dioxane (4.0 mL). The tube was evacuated and backfilled with argon (three times). The mixture was stirred at 105°C for 1 h and oxirane (1.5 mmol) was then added under an inert atmosphere. Subsequently, the mixture was stirred for 18 h at 105°C. After cooling to room temperature, the mixture was passed through silica gel pad and concentrated under reduced pressure. The resulting residue was purified with column chromatography on silica gel (eluent gradient of EtOAc/hexane, see spectroscopic analysis section) to give the products **4** in the yields listed in Tables 2 and 3.

3.2 | Preparation of compounds 5

A Schlenk tube (25 mL) equipped with a magnetic stir bar was charged with terminal alkyne (0.3 mmol), isocyanate (0.25 mmol), CuI (0.3 mmol), *t*.BuOK (0.4 mmol), 50 mg of ground 3 Å molecular sieves, and dioxane (1.0 mL). The tube was evacuated and backfilled with argon (three times). The mixture was stirred at 105°C for 5 h under an inert atmosphere. After cooling to room temperature, the mixture was passed through silica gel pad and concentrated under reduced pressure. The resulting residue was purified with column chromatography on silica gel (eluent gradient of EtOAc/hexane, see spectroscopic analysis section) to give the product **5**.

3.3 | Preparation of compounds 6

A tube (25 mL) equipped with a magnetic stir bar was charged with compound **5** (0.5 mmol), *t*.BuOK (0.7 mmol), 150 mg of ground 3 Å molecular sieves, and dioxane (2.5 mL). The tube was evacuated and backfilled with argon (three times). The mixture was then stirred for 12 h at 105°C. After cooling to room temperature, the mixture was passed through silica gel pad and concentrated under reduced pressure. The resulting residue was purified with column chromatography on silica gel (eluent gradient of EtOAc/hexane, see spectroscopic analysis section) to give the products **4a**.

3.4 | Conversion 6 to 4a

A Schlenk tube (25 mL) equipped with a magnetic stir bar was charged with compound **6** (0.5 mmol), CuI (0.05 mmol), *t*.BuOK (0.7 mmol), and dioxane (2.0 mL). The mixture was stirred for 3 h at 105°C. After cooling to room temperature, the mixture was passed through silica gel pad and concentrated under reduced pressure. The resulting residue was purified with column chromatography on silica gel (eluent gradient of EtOAc/hexane, see spectroscopic analysis section) to give the products **6**.

3.5 | 2-Benzylidene-6-ethyl-4-phenylmorpholin-3-one (4a)

The crude product was purified by column chromatography (SiO_2; Hexane/EtOAc 4/1, R_f: 0.41) affording 0.23 g (79%) of **4a**; Colorless oil. IR (KBr): $\bar{\nu}$ = 3018, 2867, 1659, 1461, 1312, 1066. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H = 1.04 (3 H, d, ^3J = 6.4 Hz, Me), 1.79–1.85 (2 H, m, 2 CH), 3.98 (1 H, dd, ^2J = 15.1 Hz, ^3J = 10.6 Hz, CH), 4.15 (1 H, dd, ^2J = 15.1 Hz, ^3J = 5.0 Hz, CH), 4.78–4.84 (1 H, m, CH), 6.52 (1 H, s, CH), 7.04 (1 H, t, ^3J = 7.4 Hz, CH), 7.26–7.33 (3 H, m, 3 CH), 7.44 (2 H, t, ^3J = 7.4 Hz, 2 CH), 7.66 (2 H, d, ^3J = 7.4 Hz, 2 CH), 7.78 (2 H, d, ^3J = 7.2 Hz, 2 CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C = 11.8 (Me), 34.2 (CH_2), 61.8 (CH_2), 80.8 (CH), 112.8 (CH), 126.3 (2 CH), 126.9 (CH), 127.4 (CH), 128.9 (2 CH), 129.5 (2 CH), 130.2 (2 CH), 133.1 (C), 145.5 (C), 148.9 (C), 165.3 (C). EI-MS (70 eV): m/z (%) = 293 (M^+, 1), 264 (11), 186 (43), 98 (87), 91 (36), 77 (100). Anal. Calcd (%) for $C_{19}H_{19}NO_2$ (293.37): C, 77.79, H, 6.53, N, 4.77. Found: C, 77. 93, H, 6.71, N, 4.90.

3.6 | 2-Benzylidene-6-isopropyl-4-phenylmorpholin-3-one (4b)

The crude product was purified by column chromatography (SiO_2; Hexane/EtOAc 5/1, R_f: 0.36) affording 0.23 g (75%) of **4b**; Colorless oil. IR (KBr): $\bar{\nu}$ = 3029, 2962, 1641, 1534, 1267, 1154. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H = 1.12 (6 H, d, ^3J = 5.0 8 Hz, 2 Me), 2.47–2.53 (1 H, m, CH), 3.97 (1 H, dd, ^2J = 14.6 Hz, ^3J = 5.8 Hz, CH), 4.11 (1 H, dd, ^2J = 14.6 Hz, ^3J = 10.9 Hz, CH), 4.56–4.61 (1 H, m, CH), 6.62 (1 H, s, CH), 7.01 (1 H, t, ^3J = 7.2 Hz, CH), 7.29 (2 H, t, ^3J = 7.2 Hz, 2 CH), 7.38 (1 H, t, ^3J = 7.7 Hz, CH), 7.46 (2 H, t, ^3J = 7.7 Hz, 2 CH), 7.61 (2 H, d, ^3J = 7.6 Hz, 2 CH), 7.80 (2 H, d, ^3J = 7.2 Hz, 2 CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C = 19.8 (2 Me), 36.7 (CH), 60.1 (CH_2), 83.4 (CH), 114.1 (CH), 126.8 (2 CH), 127.3 (CH), 127.9 (CH), 129.2 (2 CH), 129.9 (2 CH), 131.4 (2 CH), 134.2 (C), 142.5 (C), 146.8 (C), 166.1 (C). EI-MS (70 eV): m/z (%) = 307 (M^+, 1), 263 (17), 186 (35), 98 (86), 82 (71), 77 (100). Anal. Calcd (%) for $C_{20}H_{21}NO_2$ (307.39): C, 78.15; H, 6.89, N, 4.56. Found: C, 78.32; H, 7.06, N, 4.72.

3.7 | 2-Benzylidene-6-(*tert*-butyl)-4-phenylmorpholin-3-one (4c)

The crude product was purified by column chromatography (SiO_2; Hexane/EtOAc 5/1, R_f: 0.51) affording 0.24 g (74%) of **4c**; Colorless oil. IR (KBr): $\bar{\nu}$ = 3046, 2947, 1662, 1543, 1462, 1254, 1104. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H = 0.98 (9 H, s, 3 Me), 3.89 (1 H, dd, ^2J = 13.9 Hz, ^3J = 5.4 Hz, CH), 4.14 (1 H, dd, ^2J = 13.9 Hz, ^3J = 10.7 Hz, CH), 4.39 (1 H, dd, ^3J = 10.7, 5.4 Hz, CH), 6.54 (1 H, s, CH), 6.94 (1 H, t, ^3J = 7.6 Hz, CH), 7.31 (2 H, t, ^3J = 7.6 Hz, 2 CH), 7.35 (1 H, t, ^3J = 7.3 Hz, CH), 7.44 (2 H, t, ^3J = 7.3 Hz, 2 CH), 7.64 (2 H, d, ^3J = 7.3 Hz, 2 CH), 7.82 (2 H, d, ^3J = 7.6 Hz, 2 CH). ^{13}C NMR (125.7 MHz, $CDCl_3$):

δ_C = 30.3 (3 Me), 35.1 (C), 58.7 (CH_2), 96.0 (C), 113.6 (CH), 126.3 (2 CH), 127.0 (CH), 128.1 (CH), 128.7 (2 CH), 129.1 (2 CH), 130.2 (2 CH), 133.8 (C), 144.7 (C), 149.1 (C), 166.7 (C). EI-MS (70 eV): *m/z* (%) = 321 (M^+, 1), 264 (28), 186 (44), 145 (31), 98 (87), 77 (100), 57 (72). Anal. Calcd (%) for $C_{20}H_{21}NO_2$ (321.42): C, 78.47; H, 7.21, N, 4.36. Found: C, 78.69; H, 7.42, N, 4.52.

3.8 | Methyl-6-benzylidene-2-methyl-5-oxo-4-phenylmorpholine-2-carboxylate (4d)

The crude product was purified by column chromatography (SiO_2; Hexane/EtOAc 4/1, R_f: 0.19) affording 0.20 g (58%) of **4d**; Colorless oil. IR (KBr): $\bar{\nu}$ = 3033, 2972, 1735, 1660, 1534, 1311, 1082. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H = 1.65 (3 H, s, Me), 3.79 (3 H, s, OMe), 4.56 (1 H, d, ^2J = 12.2 Hz, CH), 4.71 (1 H, d, ^2J = 12.2 Hz, CH), 6.63 (1 H, s, CH), 6.96 (1 H, t, ^3J = 7.8 Hz, CH), 7.29 (2 H, t, ^3J = 7.8 Hz, 2 CH), 7.37 (1 H, t, ^3J = 7.0 Hz, CH), 7.47 (2 H, t, ^3J = 7.0 Hz, 2 CH), 7.67 (2 H, d, ^3J = 7.0 Hz, 2 CH), 7.76 (2 H, d, ^3J = 7.8 Hz, 2 CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C = 24.1 (Me), 55.7 (OMe), 67.3 (CH_2), 92.8 (C), 119.7 (CH), 126.5 (2 CH), 126.8 (CH), 127.7 (CH), 128.9 (2 CH), 129.6 (2 CH), 129.9 (2 CH), 134.1 (C), 145.1 (C), 150.6 (C), 165.8 (C), 174.1 (C). EI-MS (70 eV): *m/z* (%) = 337 (M^+, 3), 322 (9), 245 (49), 156 (62), 98 (86), 77 (100). Anal. Calcd (%) for $C_{20}H_{19}NO_4$ (337.38): C, 71.20; H, 5.68, N, 4.15. Found: C, 71.38; H, 5.51, N, 4.32.

3.9 | Methyl-6-benzylidene-5-oxo-4-phenylmorpholine-2-carboxylate (4e)

The crude product was purified by column chromatography (SiO_2; Hexane/EtOAc 3/1, R_f: 0.18) affording 0.21 g (64%) of **4e**; Colorless oil. IR (KBr): $\bar{\nu}$ = 3036, 2960, 1739, 1651, 1278, 1153. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H = 3.73 (3 H, s, OMe), 4.60 (1 H, d, ^2J = 12.9 Hz, ^3J = 10.1 Hz, CH), 4.74 (1 H, d, ^2J = 12.9 Hz, ^3J = 5.6 Hz, CH), 5.15–5.21 (1 H, m, CH), 6.69 (1 H, s, CH), 7.04 (1 H, t, ^3J = 7.4 Hz, CH), 7.28 (2 H, t, ^3J = 7.4 Hz, 2 CH), 7.39 (1 H, t, ^3J = 7.6 Hz, CH), 7.44 (2 H, t, ^3J = 7.6 Hz, 2 CH), 7.63 (2 H, d, ^3J = 7.06 Hz, 2 CH), 7.79 (2 H, d, ^3J = 7.4 Hz, 2 CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C = 55.1 (OMe), 59.8 (CH_2), 89.1 (CH), 118.1 (CH), 126.9 (2 CH), 127.3 (CH), 128.1 (CH), 128.4 (2 CH), 129.1 (2 CH), 129.5 (2 CH), 134.3 (C), 144.7 (C), 148.9 (C), 166.1 (C), 172.9 (C). EI-MS (70 eV): *m/z* (%) = 323 (M^+, 2), 292 (7), 264 (26), 188 (58), 153 (42), 98 (83), 91 (32), 77 (100). Anal. Calcd (%) for $C_{19}H_{17}NO_4$ (323.35): C, 70.58; H, 5.30, N, 4.33. Found: C, 70.74; H, 5.49, N, 4.51.

3.10 | 2-Benzylidene-6-(isopropoxymethyl)-4-phenylmorpholin-3-one (4f)

The crude product was purified by column chromatography (SiO_2; Hexane/EtOAc 5/1, R_f: 0.32) affording 0.31 g (93%) of **4f**; Colorless oil. IR (KBr): $\bar{\nu}$ = 3019, 2978, 1657, 1467, 1312, 1267, 1076. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H = 1.22 (6 H, d, ^3J = 6.6 Hz, 2 Me), 3.71 (1 H, dd, ^2J = 13.5 Hz, ^3J = 9.7 Hz, CH), 3.75 (1 H, dd, ^2J = 13.5 Hz, ^3J = 5.4 Hz, CH), 3.87–3.92 (1 H, m, CH), 4.04 (1 H, dd, ^2J = 12.9 Hz, ^3J = 9.7 Hz, CH), 4.16 (1 H, dd, ^2J = 12.9 Hz, ^3J = 5.7 Hz, CH), 4.65–4.70 (1 H, m, CH), 6.61 (1 H, s, CH), 7.04 (1 H, t, ^3J = 7.6 Hz, CH), 7.31 (2 H, t, ^3J = 7.6 Hz, 2 CH), 7.35–7.44 (3 H, m, 3 CH), 7.65 (2 H, d, ^3J = 7.6 Hz, 2 CH), 7.80 (2 H, d, ^3J = 7.9 Hz, 2 CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C = 21.8 (2 Me), 59.2 (CH_2), 69.6 (CH_2), 78.1 (CH), 82.5 (CH), 116.1 (CH), 127.0 (2 CH), 127.4 (CH), 127.9 (CH), 128.2 (2 CH), 129.2 (2 CH), 130.4 (2 CH), 134.5 (C), 144.3 (C), 149.3 (C), 166.8 (C). EI-MS (70 eV): *m/z* (%) = 337 (M^+, 1), 322 (8), 278 (17), 202 (48), 111 (83), 98 (47), 91 (39), 77 (100). Anal. Calcd (%) for $C_{21}H_{23}NO_3$ (337.42): C, 74.75; H, 6.87, N, 4.15. Found: C, 74.92; H, 6.95, N, 4.34.

3.11 | 2-Benzylidene-6-(phenoxymethyl)-4-phenylmorpholin-3-one (4 g)

The crude product was purified by column chromatography (SiO_2; Hexane/EtOAc 4/1, R_f: 0.32) affording 0.35 g (95%) of **4 g**; Colorless oil. IR (KBr): $\bar{\nu}$ = 3025, 2961, 1649, 1469, 1324, 1189, 951. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H = 4.05 (1 H, dd, ^2J = 12.9 Hz, ^3J = 8.9 Hz, CH), 4.14 (1 H, dd, ^2J = 12.9 Hz, ^3J = 5.5 Hz, CH), 4.42 (1 H, dd, ^2J = 11.7 Hz, ^3J = 9.2 Hz, CH), 4.55 (1 H, dd, ^2J = 11.7 Hz, ^3J = 5.1 Hz, CH), 4.78–4.83 (1 H, m, CH), 6.58 (1 H, s, CH), 6.89 (2 H, d, ^3J = 7.5 Hz, 2 CH), 6.98–7.04 (2 H, m, 2 CH), 7.24 (2 H, t, ^3J = 7.5 Hz, 2 CH), 7.29 (2 H, t, ^3J = 7.1 Hz, 2 CH), 7.35 (1 H, t, ^3J = 7.8 Hz, CH), 7.46 (2 H, t, ^3J = 7.8 Hz, 2 CH), 7.63 (2 H, d, ^3J = 7.8 Hz, 2 CH), 7.76 (2 H, d, ^3J = 7.1 Hz, 2 CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C = 58.7 (CH_2), 68.1 (CH_2), 81.7 (CH), 114.1 (2 CH), 115.3 (CH), 121.6 (CH), 126.9 (2 CH), 127.3 (CH), 128.0 (CH), 128.4 (2 CH), 128.7 (2 CH), 129.6 (2 CH), 130.3 (2 CH), 134.2 (C), 144.5 (C), 149.2 (C), 160.5 (C), 166.1 (C). EI-MS (70 eV): *m/z* (%) = 371 (M^+, 1), 278 (22), 202 (37), 111 (63), 98 (84), 93 (63), 77 (100). Anal. Calcd (%) for $C_{24}H_{21}NO_3$ (371.44): C, 77.61; H, 5.70, N, 3.77. Found: C, 77.82; H, 5.90, N, 3.92.

3.12 | 2-Benzylidene-4-phenylhexahydro-2*H*-benzo[b][1,4]oxazin-3(4H)-one (4 h)

The crude product was purified by column chromatography (SiO_2; Hexane/EtOAc 6/1, R_f: 0.34) affording 0.27 g (84%) of **4 h**; Colorless solid, m.p: 111–113°C. IR (KBr): $\bar{\nu}$ = 3016, 2951, 1653, 1476, 1234, 1156. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H = 1.38–2.02 (8 H, m, 8 CH), 3.88 (1 H, ddd, ^3J = 6.1 Hz, CH), 4.29 (1 H, ddd, ^3J = 6.5 Hz, CH), 6.61 (1 H, s, CH), 7.02 (1 H, t, ^3J = 7.7 Hz, CH), 7.24–7.46 (5 H, m, 5 CH), 7.65 (2 H, d, ^3J = 7.1 Hz, 2 CH), 7.80 (2 H, d, ^3J = 7.7 Hz, 2 CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C = 27.1 (CH_2), 28.5 (CH_2), 30.6 (CH_2), 35.2 (CH_2), 67.1 (CH), 88.3 (CH), 113.2 (CH), 126.5 (2 CH), 127.0 (CH), 128.3 (CH), 128.9 (2 CH), 129.7 (2 CH), 130.3 (2 CH), 135.1 (C), 141.2 (C), 146.0 (C), 167.3 (C). EI-MS (70 eV): m/z (%) = 319 (M^+, 1), 290 (19), 212 (31), 188 (57), 116 (34), 98 (83), 91 (33), 77 (100). Anal. Calcd (%) for $C_{21}H_{21}NO_2$ (319.40): C, 78.97; H, 6.63, N, 4.39. Found: C, 79.16; H, 6.82, N, 4.54.

3.13 | 6-Benzyl-2-benzylidene-4-phenylmorpholin-3-one (4i)

The crude product was purified by column chromatography (SiO_2; Hexane/EtOAc 5/1, R_f: 0.34) affording 0.28 g (79%) of **4i**; Colorless solid, m.p: 56–58°C. IR (KBr): $\bar{\nu}$ = 3041, 2972, 1652, 1438, 1279, 1161, 1023. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H = 2.93 (1 H, dd, ^2J = 12.3 Hz, ^3J = 5.1 Hz, CH), 3.11 (1 H, dd, ^2J = 12.3 Hz, ^3J = 9.5 Hz, CH), 4.03 (1 H, dd, ^2J = 11.9 Hz, ^3J = 9.6 Hz, CH), 4.18 (1 H, dd, ^2J = 11.9 Hz, ^3J = 5.2 Hz, CH), 4.71–4.77 (1 H, m, CH), 6.53 (1 H, s, CH), 6.99 (1 H, t, ^3J = 7.6 Hz, CH), 7.16–7.35 (8 H, m, 8 CH), 7.42 (2 H, t, ^3J = 7.1 Hz, 2 CH), 7.65 (2 H, d, ^3J = 7.1 Hz, 2 CH), 7.79 (2 H, d, ^3J = 7.6 Hz, 2 CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C = 42.9 (CH_2), 60.3 (CH_2), 83.5 (CH), 116.5 (CH), 125.8 (CH), 126.9 (CH), 127.1 (2 CH), 127.8 (CH), 128.1 (2 CH), 128.5 (2 CH), 129.1 (2 CH), 129.4 (2 CH), 130.7 (2 CH), 134.6 (C), 138.25 (C), 144.7 (C), 149.2 (C), 166.7 (C). EI-MS (70 eV): m/z (%) = 355 (M^+, 1), 264 (11), 188 (63), 98 (81), 91 (89), 77 (100). Anal. Calcd (%) for $C_{24}H_{21}NO_2$ (355.44): C, 81.10; H, 5.96, N, 3.94. Found: C, 81.28; H, 6.15, N, 4.14.

3.14 | 2-Benzylidene-4,5-diphenylmorpholin-3-one (4j)

The crude product was purified by column chromatography (SiO_2; Hexane/EtOAc 3/1, R_f: 0.29) affording 0.32 g (93%) of **4j**; Colorless solid, m.p: 89–91°C. IR (KBr): $\bar{\nu}$ = 3018, 2981, 1658, 1517, 1462, `1278, 1034. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H = 4.79 (1 H, dd, ^2J = 13.5 Hz, ^3J = 5.3 Hz, CH), 4.97 (1 H, dd, ^2J = 13.5 Hz, ^3J = 9.2 Hz, CH), 5.33–5.37 (1 H, m, CH), 6.64 (1 H, s, CH), 7.05 (1 H, t, ^3J = 7.8 Hz, CH), 7.26 (1 H, t, ^3J = 7.3 Hz, CH), 7.30–7.49 (9 H, m, 9 CH), 7.66 (2 H, d, ^3J = 7.3 Hz, 2 CH), 7.82 (2 H, d, ^3J = 7.8 Hz, 2 CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C = 70.1 (CH), 81.9 (CH_2), 115.2 (CH), 125.5 (CH), 125.9 (2 CH), 126.4 (CH), 126.8 (2 CH), 127.4 (CH), 128.3 (2 CH), 129.2 (2 CH), 129.8 (2 CH), 130.1 (2 CH), 130.5 (2 CH), 134.1 (C), 140.3 (C), 144.2 (C), 150.7 (C), 166.2 (C). EI-MS (70 eV): m/z (%) = 341 (M^+, 1), 264 (23), 188 (41), 173 (46), 98 (81), 91 (37), 77 (100). Anal. Calcd (%) for $C_{23}H_{19}NO_2$ (341.41): C, 80.92; H, 5.61, N, 4.10. Found: C, 81.15; H, 5.80, N, 4.28.

3.15 | 2-Benzylidene-4-phenyl-5-(*o*-tolyl) morpholin-3-one (4 k)

The crude product was purified by column chromatography (SiO_2; Hexane/EtOAc 3/1, R_f: 0.41) affording 0.18 g (52%) of **4 k**; Colorless solid, m.p: 64–66°C. IR (KBr): $\bar{\nu}$ = 3042, 2981, 1655, 1532, 1468, 1316, 1162, 1021. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H = 2.32 (3 H, s, Me), 4.61 (1 H, dd, ^2J = 13.1 Hz, ^3J = 5.0 Hz, CH), 4.73 (1 H, dd, ^2J = 13.1 Hz, ^3J = 10.3 Hz, CH), 5.13–5.18 (1 H, m, CH), 6.58 (1 H, s, CH), 6.90 (1 H, d, ^3J = 7.3 Hz, CH), 6.97 (1 H, t, ^3J = 7.0 Hz, CH), 7.18 (1 H, t, ^3J = 7.5 Hz, CH), 7.22 (1 H, t, ^3J = 7.5 Hz, CH), 7.25–7.36 (4 H, m, 4 CH), 7.47 (2 H, t, ^3J = 7.8 Hz, 2 CH), 7.61 (2 H, d, ^3J = 7.8 Hz, 2 CH), 7.79 (2 H, d, ^3J = 7.5 Hz, 2 CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C = 21.7 (Me), 68.3 (CH), 79.2 (CH_2), 115.7 (CH), 122.1 (CH), 124.3 (CH), 126.1 (CH), 127.0 (2 CH), 127.8 (CH), 128.0 (CH), 128.5 (2 CH), 128.9 (2 CH), 129.2 (2 CH), 131.1 (CH), 133.4 (C), 136.8 (C), 140.1 (C), 143.4 (C), 149.5 (C), 166.7 (C). EI-MS (70 eV): m/z (%) = 355 (M^+, 1), 264 (16), 188 (37), 159 (60), 98 (85), 91 (34), 77 (100). Anal. Calcd (%) for $C_{24}H_{21}NO_2$ (355.44): C, 80.10; H, 5.96, N, 3.94. Found: C, 80.27; H, 6.12, N, 4.12.

3.16 | 2-Benzylidene-4-phenyl-5-(*p*-tolyl) morpholin-3-one (4 l)

The crude product was purified by column chromatography (SiO_2; Hexane/EtOAc 3/1, R_f: 0.38) affording 0.33 g (93%) of **4 l**; Colorless solid, m.p: 101–103°C. IR (KBr): $\bar{\nu}$ = 3036, 2979, 1662, 1441, 1267, 1165, 1032. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H = 2.24 (3 H, s, Me), 4.64 (1 H, dd, ^2J = 12.0 Hz, ^3J = 5.3 Hz, CH), 4.70 (1 H, dd, ^2J = 12.0 Hz, ^3J = 8.9 Hz, CH), 5.01–5.05 (1 H, m, CH), 6.56 (1 H, s, CH), 6.97 (1 H, t, ^3J = 7.7 Hz, CH), 7.14 (2

H, d, ^3J = 7.2 Hz, 2 CH), 7.25 (2 H, d, ^3J = 7.2 Hz, CH), 7.28–7.40 (5 H, m, 5 CH), 7.63 (2 H, d, ^3J = 7.7 Hz, 2 CH), 7.80 (2 H, d, ^3J = 7.1 Hz, 2 CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C = 23.5 (Me), 66.1 (CH), 79.3 (CH_2), 115.2 (CH), 126.3 (2 CH), 127.1 (CH), 127.5 (2 CH), 127.9 (CH), 128.2 (2 CH), 128.9 (2 CH), 129.3 (2 CH), 130.8 (2 CH), 133.1 (C), 138.5 (C), 139.8 (C), 141.3 (C), 147.2 (C), 166.2 (C). EI-MS (70 eV): m/z (%) = 355 (M^+, 2), 278 (9), 188 (36), 175 (57), 98 (87), 91 (42), 77 (100). Anal. Calcd (%) for $C_{24}H_{21}NO_2$ (355.44): C, 80.10; H, 5.96, N, 3.94. Found: C, 79.98; H, 5.82, N, 3.99.

3.17 | 2-Benzylidene-5-(4-bromophenyl)-4-phenylmorpholin-3-one (4 m)

The crude product was purified by column chromatography (SiO_2; Hexane/EtOAc 3/1, R_f: 0.16) affording 0.39 g (94%) of **4 m**; Colorless solid, m.p: 100–102°C. IR (KBr): $\bar{\nu}$ = 3036, 2982, 1658, 1436, 1312, 1163, 1042. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H = 4.81 (1 H, dd, ^2J = 13.4 Hz, ^3J = 5.6 Hz, CH), 4.96 (1 H, dd, ^2J = 13.4 Hz, ^3J = 9.5 Hz, CH), 5.22–5.26 (1 H, m, CH), 6.64 (1 H, s, CH), 6.92 (1 H, t, ^3J = 7.3 Hz, CH), 7.19 (2 H, d, ^3J = 7.6 Hz, 2 CH), 7.31 (2 H, t, ^3J = 7.3 Hz, CH), 7.37 (1 H, t, ^3J = 7.8 Hz, CH), 7.45 (2 H, d, ^3J = 7.8 Hz, 2 CH), 7.66 (2 H, d, ^3J = 7.8 Hz, 2 CH), 7.78 (2 H, d, ^3J = 7.3 Hz, 2 CH), 7.91 (2 H, d, ^3J = 7.6 Hz, 2 CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C = 69.3 (CH), 80.1 (CH_2), 115.7 (CH), 120.4 (C), 126.8 (2 CH), 127.3 (CH), 127.7 (2 CH), 128.5 (CH), 128.9 (2 CH), 129.7 (2 CH), 130.5 (2 CH), 132.7 (2 CH), 133.6 (C), 140.1 (C), 143.5 (C), 149.1 (C), 166.7 (C). EI-MS (70 eV): m/z (%) = 421 (M^+, 4), 419 (M^+, 4), 332 (9), 330 (9), 254 (32), 252 (32), 175 (57), 98 (87), 91 (28), 77 (100). Anal. Calcd (%) for $C_{23}H_{18}BrNO_2$ (420.31): C, 65.73; H, 4.32, N, 3.33. Found: C, 65.90; H, 4.50, N, 3.51.

3.18 | 2-Benzylidene-4-isopropyl-6-methylmorpholin-3-one (4n)

The crude product was purified by column chromatography (SiO_2; Hexane/EtOAc 6/1, R_f: 0.34) affording 0.21 g (83%) of **4n**; Colorless oil. IR (KBr): $\bar{\nu}$ = 3011, 2935, 1651, 1542, 1471, 1255, 1067. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H = 1.23 (6 H, d, ^3J = 6.1 Hz, 2 Me), 1.34 (3 H, d, ^3J = 6.2 Hz, Me), 3.41 (1 H, dd, ^2J = 11.7 Hz, ^3J = 10.0 Hz, CH), 3.58 (1 H, dd, ^2J = 11.7 Hz, ^3J = 5.3 Hz, CH), 3.99–4.04 (1 H, m, CH), 4.56–4.61 (1 H, m, CH), 6.43 (1 H, s, CH), 7.30 (1 H, t, ^3J = 7.6 Hz, CH), 7.45 (2 H, t, ^3J = 7.6 Hz, 2 CH), 7.62 (2 H, d, ^3J = 7.6 Hz, 2 CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C = 20.3 (Me), 22.5 (2 Me), 51.1 (CH_2), 60.6 (CH), 79.3 (CH), 114.2 (CH), 127.3 (CH), 128.2 (2 CH), 129.7 (2 CH), 134.8 (C), 150.1 (C), 167.8 (C). EI-MS (70 eV): m/z (%) = 245 (M^+, 1), 230 (9), 202 (17), 126 (34), 112 (63), 98 (84), 77 (100). Anal. Calcd (%) for $C_{15}H_{19}NO_2$ (245.32): C, 73.44, H, 7.81, N, 5.71. Found: C, 73. 62, H, 7.95, N, 5.87.

3.19 | 2-Benzylidene-4-cyclohexyl-6-methylmorpholin-3-one (4o)

The crude product was purified by column chromatography (SiO_2; Hexane/EtOAc 5/1, R_f: 0.35) affording 0.24 g (84%) of **4o**; Colorless solid, m.p: 82–84°C. IR (KBr): $\bar{\nu}$ = 3021, 2935, 1652, 1435, 1311, 1178, 1054. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H = 1.27 (3 H, d, ^3J = 6.3 Hz, Me), 1.35–1.87 (10 H, m, 5 CH_2), 3.52 (1 H, dd, ^2J = 13.2 Hz, ^3J = 10.1 Hz, CH), 3.65 (1 H, dd, ^2J = 13.2 Hz, ^3J = 5.1 Hz, CH), 3.77–3.82 (1 H, m, CH), 4.61–4.67 (1 H, m, CH), 6.49 (1 H, s, CH), 7.32 (1 H, t, ^3J = 7.8 Hz, CH), 7.48 (2 H, t, ^3J = 7.8 Hz, 2 CH), 7.67 (2 H, d, ^3J = 7.8 Hz, 2 CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C = 20.1 (Me), 24.1 (CH_2), 27.3 (CH_2), 29.4 (CH_2), 30.8 (CH_2), 36.6 (CH_2), 53.5 (CH_2), 66.8 (CH), 79.1 (CH), 115.5 (CH), 126.8 (CH), 128.7 (2 CH), 129.5 (2 CH), 134.1 (C), 150.6 (C), 168.6 (C). EI-MS (70 eV): m/z (%) = 285 (M^+, 3), 270 (12), 181 (34), 112 (47), 98 (83), 83 (71), 77 (100). Anal. Calcd (%) for $C_{18}H_{23}NO_2$ (285.39): C, 75.76, H, 8.12, N, 4.91. Found: C, 75. 91, H, 8.28, N, 5.12.

3.20 | 6-Methyl-2-(4-methylbenzylidene)-4-phenylmorpholin-3-one (4p)

The crude product was purified by column chromatography (SiO_2; Hexane/EtOAc 5/1, R_f: 0.36) affording 0.23 g (80%) of **4p**; Colorless solid, m.p: 81–83°C. IR (KBr): $\bar{\nu}$ = 3018, 2971, 1647, 1445, 1278, 1106, 1032. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H = 1.33 (3 H, s, Me), 2.58 (3 H, s, Me), 4.01 (1 H, dd, ^2J = 12.8 Hz, ^3J = 10.1 Hz, CH), 4.14 (1 H, dd, ^2J = 12.8 Hz, ^3J = 4.9 Hz, CH), 4.67–4.73 (1 H, m, CH), 6.61 (1 H, s, CH), 7.01 (1 H, t, ^3J = 7.4 Hz, CH), 7.30 (2 H, t, ^3J = 7.4 Hz, 2 CH), 7.46 (2 H, d, ^3J = 7.8 Hz, 2 CH), 7.65 (2 H, d, ^3J = 7.8 Hz, 2 CH), 7.79 (2 H, d, ^3J = 7.4 Hz, 2 CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C = 21.2 (Me), 24.3 (Me), 68.8 (CH_2), 80.1 (CH), 115.1 (CH), 127.3 (2 CH), 127.8 (CH), 129.1 (2 CH), 129.9 (2 CH), 130.7 (2 CH), 131.4 (C), 139.2 (C), 144.7 (C), 150.1 (C), 165.8 (C). EI-MS (70 eV): m/z (%) = 293 (M^+, 2), 278 (13), 202 (27), 175 (49), 112 (62), 98 (87), 91 (34), 77 (100). Anal. Calcd (%) for $C_{19}H_{19}NO_2$ (293.37): C, 77.79; H, 6.53, N, 4.77. Found: C, 77.96; H, 6.74, N, 4.93.

3.21 | 6-Methyl-2-(4-methylbenzylidene)-4-(*p*-tolyl)morpholin-3-one (4q)

The crude product was purified by column chromatography (SiO_2; Hexane/EtOAc 5/1, R_f: 0.44) affording 0.27 g (87%) of **4q**; Colorless solid, m.p: 84–86°C. IR (KBr): $\bar{\nu}$ = 3034, 2972, 1657, 1543, 1455, 1267, 1152, 1032. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H = 1.35 (3 H, s, Me), 2.39 (3 H, s, Me), 2.51 (3 H, s, Me), 3.93 (1 H, dd, ^2J = 12.1 Hz, ^3J = 10.0 Hz, CH), 4.04 (1 H, dd, ^2J = 12.1 Hz, ^3J = 5.2 Hz, CH), 4.46–4.51 (1 H, m, CH), 6.53 (1 H, s, CH), 7.11 (2 H, d, ^3J = 7.6 Hz, 2 CH), 7.28 (2 H, d, ^3J = 7.4 Hz, 2 CH), 7.43 (2 H, d, ^3J = 7.1 Hz, 2 CH), 7.61 (2 H, d, ^3J = 7.1 Hz, 2 CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C = 20.1 (Me), 22.3 (Me), 24.3 (Me), 67.1 (CH_2), 79.6 (CH), 115.3 (CH), 127.9 (2 CH), 129.3 (2 CH), 129.6 (2 CH), 130.9 (C), 135.1 (2 CH), 135.1 (C), 138.6 (C), 141.3 (C), 149.4 (C), 166.1 (C). EI-MS (70 eV): *m*/*z* (%) = 307 (M^+, 3), 292 (18), 189 (42), 162 (28), 98 (87), 91 (34), 91 (34), 77 (100). Anal. Calcd (%) for $C_{20}H_{21}NO_2$ (307.39): C, 78.15; H, 6.89, N, 4.56. Found: C, 78.32; H, 6.71, N, 4.73.

3.22 | 4-(4-Methoxyphenyl)-6-methyl-2-(4-methylbenzylidene)morpholin-3-one (4r)

The crude product was purified by column chromatography (SiO_2; Hexane/EtOAc 6/1, R_f: 0.31) affording 0.30 g (92%) of **4r**; Colorless solid, m.p: 98–100°C. IR (KBr): $\bar{\nu}$ = 3033, 2973, 1651, 1452, 1311, 1252, 1087. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H = 1.31 (3 H, s, Me), 2.52 (3 H, s, Me), 3.89 (3 H, s, OMe), 3.83 (1 H, dd, ^2J = 13.6 Hz, ^3J = 11.5 Hz, CH), 3.94 (1 H, dd, ^2J = 13.6 Hz, ^3J = 5.3 Hz, CH), 4.53–4.59 (1 H, m, CH), 6.59 (1 H, s, CH), 6.90 (2 H, d, ^3J = 7.8 Hz, 2 CH), 7.43 (2 H, d, ^3J = 7.2 Hz, 2 CH), 7.65 (2 H, d, ^3J = 7.2 Hz, 2 CH), 7.98 (2 H, d, ^3J = 7.8 Hz, 2 CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C = 20.7 (Me), 24.2 (Me), 56.1 (OMe), 63.8 (CH_2), 76.3 (CH), 114.1 (2 CH), 116.2 (CH), 124.1 (2 CH), 129.1 (2 CH), 129.8 (2 CH), 131.3 (C), 137.1 (C), 139.4 (C), 149.6 (C), 159.7 (C), 165.3 (C). EI-MS (70 eV): *m*/*z* (%) = 323 (M^+, 3), 308 (9), 205 (19), 203 (38), 107 (70), 98 (87), 91 (34), 77 (100). Anal. Calcd (%) for $C_{20}H_{21}NO_3$ (323.39): C, 74.28; H, 6.55, N, 4.33. Found: C, 74.45; H, 6.68, N, 4.50.

3.23 | 2-(4-Methoxybenzylidene)-6-methyl-4-phenylmorpholin-3-one (4 s)

The crude product was purified by column chromatography (SiO_2; Hexane/EtOAc 7/1, R_f: 0.25) affording 0.24 g (78%) of **4 s**; Colorless solid, m.p: 116–118°C. IR (KBr): $\bar{\nu}$ = 3042, 2972, 1655, 1472, 1243, 1032. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H = 1.35 (3 H, s, Me), 3.84 (3 H, s, OMe), 3.95 (1 H, dd, ^2J = 12.0 Hz, ^3J = 9.3 Hz, CH), 4.06 (1 H, dd, ^2J = 12.0 Hz, ^3J = 4.9 Hz, CH), 4.50–4.56 (1 H, m, CH), 6.50 (1 H, s, CH), 7.03 (1 H, t, ^3J = 7.7 Hz, CH), 7.12 (2 H, d, ^3J = 7.5 Hz, 2 CH), 7.38 (2 H, t, ^3J = 7.7 Hz, 2 CH), 7.61 (2 H, d, ^3J = 7.5 Hz, 2 CH), 7.70 (2 H, d, ^3J = 7.7 Hz, 2 CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C = 21.8 (Me), 56.1 (OMe), 65.6 (CH_2), 79.1 (CH), 114.1 (2 CH), 115.3 (CH), 125.1 (C), 127.3 (2 CH), 128.1 (2 CH), 129.6 (2 CH), 133.9 (2 CH), 142.1 (C), 149.8 (C), 160.1 (C), 166.1 (C). EI-MS (70 eV): *m*/*z* (%) = 309 (M^+, 1), 295 (8), 218 (34), 175 (51), 122 (88), 98 (80), 91 (34), 77 (100). Anal. Calcd (%) for $C_{19}H_{19}NO_3$ (309.37): C, 73.77; H, 6.19, N, 4.53. Found: C, 73.94; H, 6.37, N, 4.68.

3.24 | 2-(4-Methoxybenzylidene)-6-methyl-4-(4-nitrophenyl)morpholin-3-one (4 t)

The crude product was purified by column chromatography (SiO_2; Hexane/EtOAc 1/1, R_f: 0.38) affording 0.07 g (21%) of **4 t**; Colorless solid, m.p: 176–178°C. IR (KBr): $\bar{\nu}$ = 3028, 2988, 1653, 1552, 1467, 1345, 1211, 1165. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H = 1.32 (3 H, s, Me), 3.90 (3 H, s, OMe), 4.07 (1 H, dd, ^2J = 13.5 Hz, ^3J = 9.8 Hz, CH), 4.19 (1 H, dd, ^2J = 13.5 Hz, ^3J = 5.5 Hz, CH), 4.58–4.63 (1 H, m, CH), 6.54 (1 H, s, CH), 7.13 (2 H, d, ^3J = 7.4 Hz, 2 CH), 7.47 (2 H, d, ^3J = 7.8 Hz, 2 CH), 7.71 (2 H, d, ^3J = 7.4 Hz, 2 CH), 8.17 (2 H, d, ^3J = 7.8 Hz, 2 CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C = 21.2 (Me), 56.8 (OMe), 67.1 (CH_2), 80.9 (CH), 114.7 (2 CH), 116.9 (CH), 124.9 (2 CH), 125.7 (C), 131.8 (2 CH), 133.7 (2 CH), 144.7 (C), 149.8 (C), 150.3 (C), 160.1 (C), 166.7 (C). EI-MS (70 eV): *m*/*z* (%) = 354 (M^+, 1), 340 (11), 219 (37), 146 (28), 122 (67), 98 (83), 91 (34), 77 (100). Anal. Calcd (%) for $C_{19}H_{18}N_2O_5$ (354.36): C, 64.40; H, 5.12, N, 7.91. Found: C, 64.59; H, 5.31, N, 7.78.

3.25 | *N*,3-diphenylpropiolamide (5)

The crude product was purified by column chromatography (SiO_2; Hexane/EtOAc 2/1, R_f: 0.38) affording 0.20 g (92%) of **5**; Colorless solid, m. p: 81–81°C. IR (KBr): $\bar{\nu}$ = 3341, 3043, 2971, 1658, 1532, 1467, 1231. ^{1}H NMR (500.1 MHz, Acetone-d_6): δ_H = 7.11 (1 H, t, ^3J = 7.8 Hz, CH), 7.29 (2 H, t, ^3J = 7.8 Hz, 2 CH), 7.38–7.44 (3 H, m, 3 CH), 7.54 (2 H, d, ^3J = 7.9 Hz, 2 CH), 7.65 (2 H, d, ^3J = 7.8 Hz, 2 CH), 8.35 (1 H, br s, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C = 83.5 (C), 98.8 (C), 120.3 (C), 123.9 (2 CH), 127.1 (CH), 127.9 (CH), 129.1 (2 CH), 130.8 (2 CH), 133.4 (2 CH), 138.5 (C), 148.2 (C). EI-MS

(70 eV): m/z (%) = 221 (M^+, 1), 144 (46), 129 (21), 101 (76), 77 (100). Anal. Calcd (%) for $C_{15}H_{11}NO$ (221.26): C, 81.43, H, 5.01, N, 6.33. Found: C, 81. 60, H, 5.18, N, 6.48.

3.26 | *N*-(2-hydroxybutyl)-*N*,3-diphenylpropiolamide (6)

The crude product was purified by column chromatography (SiO_2; Hexane/EtOAc 4/1, R_f: 0.29) affording 0.07 g (23%) of **6**; Colorless oil. IR (KBr): $\bar{\nu}$ = 3432, 3031, 2967, 2256, 1653, 1532, 1432, 1221, 1092. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H = 0.91 (3 H, d, ^3J = 5.8 Hz, Me), 1.55–1.63 (2 H, m, 2 CH), 3.74 (1 H, dd, ^2J = 12.3 Hz, ^3J = 9.0 Hz, CH), 4.01 (1 H, dd, ^2J = 12.3 Hz, ^3J = 5.2 Hz, CH), 4.26–4.32 (1 H, m, CH), 4.74 (1 H, br s, OH), 6.92 (1 H, t, ^3J = 7.2 Hz, CH), 7.29 (2 H, t, ^3J = 7.2 Hz, 2 CH), 7.40 (2 H, t, ^3J = 7.8 Hz, 2 CH), 7.51 (1 H, t, ^3J = 7.9 Hz, CH), 7.59 (2 H, d, ^3J = 7.8 Hz, 2 CH), 7.81 (2 H, d, ^3J = 7.2 Hz, 2 CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C = 11.2 (Me), 32.6 (CH_2), 59.3 (CH_2), 73.1 (CH), 90.1 (C), 98.2 (C), 119.4 (C), 126.9 (2 CH), 126.9 (CH), 127.1 (CH), 127.9 (CH), 129.2 (2 CH), 130.5 (2 CH), 132.9 (2 CH), 140.9 (C), 145.9 (C). EI-MS (70 eV): m/z (%) = 293 (M^+, 1), 264 (8), 220 (31), 129 (73), 92 (80), 77 (100). Anal. Calcd (%) for $C_{19}H_{19}NO_2$ (293.37): C, 77.79, H, 6.53, N, 4.77. Found: C, 77. 62, H, 6.42, N, 4.86.

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